CLAIMS

1. A compound of formula I:

$$\begin{array}{c|cccc}
R^1 \\
N & Z^1 \\
R^2 \\
Z^2 & B & N \\
Q^1 & R^3
\end{array}$$

or a pharmaceutically acceptable salt thereof, wherein:

R¹ is halogen, CN, NO₂, or V_mR;

 Z^1 and Z^3 are each independently N or CR^2 , and Z^2 is N or CR^1 , provided that Z^1 , Z^2 and Z^3 are not simultaneously N;

each occurrence of R^Z is independently halogen, CN, NO₂, or U_nR';

 R^2 is U_nR' ;

X¹ and X² are each independently CR⁴ or N;

each occurrence of R⁴ is independently halogen, CN, NO₂, or V_mR;

each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-;

m and n are each independently 0 or 1;

each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or

sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; Q^1 is -CO-, $-SO_2$ -, -CONR-, or $-SO_2NR$ -; R^3 is O^2 - Ar^1 .

or R² and Q¹-R³, taken together with the nitrogen atom, form the cyclic group:

, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO₂-, -O-, -S-, -NR⁵-, or -C(R⁵)₂-, and R⁵ is U_nR^7 ;

 Q^2 and Q^3 are each independently a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by -NR'-, -S-, - O-, -CS-, $-CO_2$ -, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2$ -, $-SO_2NR'$ -, - $NR'SO_2$ -, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, $-NR'SO_2NR'$ -, -SO-, $-SO_2$ -, $-PO_2$ -, or -POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, CN, NO_2 , or U_nR' , or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar¹ and Ar² are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ and Ar² are each optionally substituted with 0-5 independent occurrences of TR³; wherein T is a bond or is a C₁-C6 alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R³ is independently R³, halogen, NO₂, or CN; provided that:

I. for compounds described where
$$\frac{B}{S}$$
 is $\frac{A}{X_2-X_1}$, one or more of, or all of the following conditions apply:

$$\begin{array}{c|c}
R^1 \\
S \\
N \\
N \\
N \\
N
\end{array}$$

$$\begin{array}{c}
R^2 \\
R^3 \\
R^3
\end{array}$$

A) for compounds having the structure:

- i) when R^1 is Cl, and R^2 is $-CH(CH_3)COOCH_3$ or hydrogen, then Q^1-R^3 is not $-CO(unsubstituted\ phenyl)$, $-CO(unsubstituted\ 2-furyl)$, or $-COCH_2(unsubstituted\ phenyl)$;
 - ii) when R¹ is hydrogen, R² is hydrogen, and Q¹ is -CO-, then R³ is not:
 - a) phenyl substituted with 4-O(CH₂)₄₋₇CH₃ or 4-(CH₂)₄₋₇CH₃;;
 - b) phenyl substituted with 2-Cl, 4-NO₂, 4-Cl, 2-Br, 3-Br, 3-I, 3-CH₃, 4-OCH₃, 3-NO₂, or 4-I;
 - c) 2,6-OCH₃-phenyl
 - d) (5-Cl, 3-CH₃, 1-phenyl)- pyrazol-4-yl; or
 - e) 4-OnBu-phenyl, -CH₂O(2-F-phenyl), -(CH₂)₂phenyl, furan-2-yl, thiophen-2-yl, 4-CH₃-phenyl, -CH₂O(2-CH₃-phenyl), 3-OCH₃-phenyl, 2-(2,5-dimethoxylphenyl)quinolin-4-yl, -NH-(4-Cl-phenyl), -NH-(3,4-dichlorophenyl), (2-CO₂H, 3-NO₂)-phenyl, 3,5-dimethyl-ixoxazol-4-yl, -CH=CH-phenyl, 4-F-phenyl, C(CH₃)₂O-(4-Cl-phenyl), -NH(3-Cl-phenyl), -NHphenyl, unsubstituted phenyl, 3,4,5-OCH₃-phenyl, 4-NO₂-phenyl, 4-cyclopentoxy-phenyl, -(CH₂)₃phenyl, -(CH₂)₃phenyl, -(tricyclo[3.3.1.13,7]decan-1-yl, -CH₂O-(3-CH₃-phenyl), 3-NO₂-phenyl, -cyclopropyl-(4-tert-butyl-phenyl), 2,3-OCH₃-phenyl, 1,3-benzodioxo-5-yl, -CH₂-O-(4-F-phenyl), or 3-Br-phenyl;
- iii) when R^1 is hydrogen, R^2 is hydrogen, and Q^1 is -CSNH-, then R^3 is not 2,3,4,6-tetra-O-acetyl- \square -D-glucopyranosyl;
- iv) when R¹ is hydrogen, R² is hydrogen, and Q¹ is SO₂, then R³ is not unsubstituted phenyl, unsubstituted benzyl, unsubstituted naphthyl, phenyl substituted with para-NHCOCH₃, para-NH₂, or para-CH₃; and

- v) when R^1 is hydrogen, R^2 is $-CH_2CH=CH_2$, and Q^1 is CO, then R^3 is not 4-OCH₃-phenyl, unsubstituted naphthyl, -NH-(4-OCH₃-phenyl), 3,5-OCH₃-phenyl, -CH₂Ophenyl, -CH₂-thiophen-2-yl, or -CH(phenyl)(CH₂CH₃); and
- vi) when R^1 is hydrogen, R^2 is CH_2CH_3 , and Q^1 is CO, then R^3 is not 2,4-Cl-phenyl; and

B) for compounds having the structure: , when
$$R^2$$
 is hydrogen or CH^3 , and Q^1 is $-CO$ -, then R^3 is not $-OCH_2CH_2OCH_2$ phenyl;

II. for compounds described where X_1-S , one or more of, or all of the following conditions apply:

A) for compounds having the structure:

i) when R³ is Q²-Ar¹, and Q² is a bond then Ar¹ is not any one or more of the following: unsubstituted phenyl or phenyl substituted with 2-Br; 2-Cl; 2-I; 2,6-F; 3,5-OCH₃; 3,4,5-OCH₃; 2,4-OCH₃; 3,4-CH₃; 2,5-Cl; 3,4,-OCH₃; 2-Cl, 5-NO₂; 3,5-Cl; 3-O(CH₂)₄CH₃, 3-O-n-butyl, 3-CF₃, 3-OCH₃, 3-Br; 3-NO₂; 3-CH₃; 3-O-phenyl; 3-Cl; 4-N(CH₃)₂; 4-N(CH₂CH₃)₂; 4-SO₂N(R')₂; 4-CN; 4-COOCH₃; 4-C(O)phenyl; 4-phenyl; 4-tert-butyl, 4-O-phenyl; 4-O-isopropyl; 4-OCH₃; 4-OCH₂CH₃; 4-O-n-butyl; 4-Cl; 4-Br; 4-F; 4-CH₃; 4-NO₂; 4-Cl; 3-NO₂, 4-morpholino; 3-NO₂, 2,5-dioxopyrrolidinyl, or 4-piperidinyl; and

ii) R³ is not any one or more of the following groups:

-CH=CH(thiophen-2-yl), -CH=CH-unsubstituted phenyl, -

CH₂(3-NHCOPh-phenyl), -6-bromo-2-(4-ethylphenyl)-4-quinolinyl, -CH₂-pyrrolidine,

unsubstituted cyclohexyl, unsubstituted benzyl, unsubstituted furan-2-yl, -CH=CH(3-NO₂-phenyl), -CH=CH(4-NO₂-phenyl), -CH₂-naphthyl, unsubstituted naphthyl, unsubstituted thiophene, unsubstituted cyclopropyl, 1,4-benzodioxin, 2-oxo-1-benzopyran, 4-oxo-1-benzopyran, 2-thienyl-quinolin-4-yl, 3-chloro-benzo[b]thiophen-2-yl, 5-Br-(thiophen-2-yl), 5-Cl-(thiophen-2-yl), 5-NO₂-(thiophen-2-yl), 5-NO₂-(furan-2-yl), 2,5-Cl-(thiophen-3-yl), -CH=CH-(5-NO₂-thiophen-2-yl), 5-NO₂-(benzothiophen-2-yl), 3-OCH₃-(naphth-2-yl), -CH₂O(2,4-Cl-phenyl), -(CH₂)₂S-phenyl, 2-phenyl-quinolin-4-yl, -CH₂O(4-Cl-phenyl), -CH₂CH₂-3-(4-Cl-phenyl)-1-phenyl-1-H-pyrazol-4-yl, or -CH₂(1,3-dioxoisoindole); and

B) for compounds having the structure:

- i) when R^1 is Cl, and X_1 is C-Cl, then R^3 is not NHSO₂-(2-CF₃-phenyl) or NHSO₂-(2,6-dimethoxy-phenyl);
- ii) when R^1 is CH_3 , and X_1 is $C-CH_3$, then R^3 is not an optionally substituted indole or optionally substituted dihydroindole; and
- C) for compounds of general formula I, when Z_1 , Z_2 and Z_3 are each CH, R^1 is H, X^1 is CH and X_2 is C-COOCH₃, then R^3 is not 2-(4-ethyl-phenyl)-6-bromo-quinolin-4-yl; and

III. for compounds described above where is S-X₁, one or more of, or all of the following conditions apply:

- A) when Z^1 , Z^2 and Z^3 are each CH, X^2 is N, X^1 is CH, Q^1 is -CONR-, and R^2 is hydrogen or -CH₃, then R^3 is not optionally substituted pyridyl, optionally substituted thiazol-4-yl, -CH₂pyridyl, benzimidazol-4-yl, quinolin-2-yl, 1-bromo-isoquinolin-3-yl, benzthiazol-2-yl, optionally substituted 5,6,7,8-tetrahydro-naphthyridin-2-yl, or phenyl substituted with -CH₂piperidinyl; and
- B) when Z^1 , Z^2 and Z^3 are each CH, X^2 is N, X^1 is CH, Q^1 is SO_2 , and R^2 is hydrogen, then R^3 is not phenyl substituted with A0 where A1 where A2 is hydrogen or COCH3;

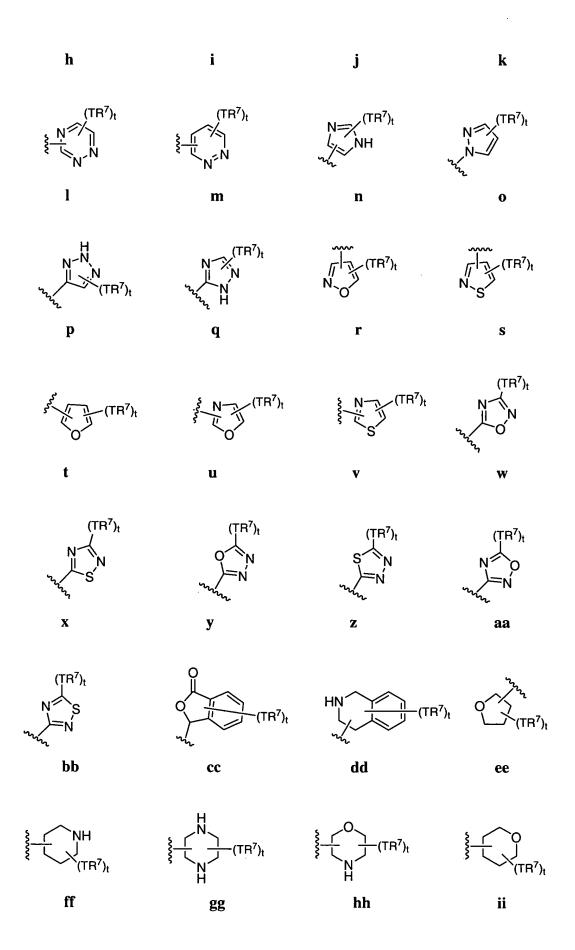
- C) when Z^1 , Z^2 and Z^3 are each CH, X_1 is C-CO₂H, X^2 is CH, R^2 is hydrogen, and Q^1 is SO₂, then R^3 is not 2-CH₃-phenyl; and
- D) when Z^1 , Z^2 and Z^3 are each CH, X_1 is CH, X^2 is N, R^2 is hydrogen, and Q^1 is CO, then R^3 is not 5-methoxy-6-trifluoromethyl-1H-indole.
- 2. The compound of claim 1, wherein the compound has one of the structures:

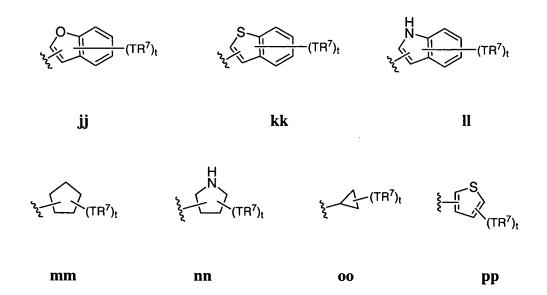
3. The compound of claim 1, wherein R^3 is Q^2 -Ar¹ and compounds have one of formulas I-A-i, I-B-i, or I-C-i:

- 4. The compound of claim 3, wherein R^2 is hydrogen, or is U_nR' , where n is 1, and U is a C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by O, NR, S, or C(O).
- 5. The compound of claim 3, wherein U is -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂-, and preferred R' groups are hydrogen, C₁-C₄alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R', taken together

with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered heterocyclyl ring.

- 6. The compound of claim 3, wherein Q^1 is -C(O)- or $-SO_2NR$ -.
- 7. The compound of claim 3, wherein Q^2 is a direct bond, or is $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, $-(CHR^6)_{q^-}$, or $-(CHR^6)_{q^-}$, or $-(CHR^6)_{q^-}$, wherein q is 0, 1, 2, or 3, and R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}OR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring.
- 8. The compound of claim 7, wherein R⁶ is CH₂OH, CH₂CH₂OH, OH, OMe, OEt, NH₂, NH(Me), NH(Et), N(Me)(Me), CH₂NH₂, CH₂CH₂NH₂, NHCO₂t-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, NH(CH₂)₃NH₂, NH(CH₂)₂NH₂, NH(CH₂)₂NHEt, NHCH₂pyridyl, NHSO₂phenyl, NHC(O)CH₂C(O)Ot-butyl, NHC(O)CH₂NH₃, and NHCH₂-imidazol-4-yl.
- 9. The compound of claim 3, wherein Ar¹ is:



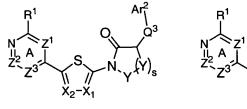


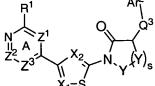
wherein t is 0, 1, 2, 3, 4 or 5, and wherein any Ar^1 is bonded to Q^2 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7 .

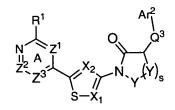
- 10. The compound of claim 9, wherein Ar¹ is a, b, e, g, h, i, j, k, r, cc, dd, ff, jj, ll, or pp.
- 11. The compound of claim 9, wherein T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by -O-, -NR-, -S-, $-SO_2$ -, -COO-, -CO-, $-OSO_2$ -, $-NRSO_2$, -CONR-, or $-SO_2NR$ -, and R^7 is R' or halogen.
- 12. The compound of claim 9, wherein each occurrence of TR^7 is independently $-C_{1.3}$ alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, -C(O)N(R)(R'), -C(O)N(R)(R'), -C(O)N(R)(R'), $-C(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)_2N(R)(R')$, or $-O(CH_2)_2N(R)(R')$, $-(CH_2)_2N(R)(R')$, or $-O(CH_2)_2N(R)(R')$, $-(CH_2)_2N(R)(R')$, or $-O(CH_2)_2N(R)(R')$, or $-O(CH_2$

13. The compound of claim 1, wherein R^3 is Q^2 -Ar¹, or R^2 and Q^1 -R³, taken together with

the nitrogen atom, form the cyclic group: $(Y)_s$, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO₂-, -O-, -S-, -NR⁵-, or -C(R⁵)₂-, and R⁵ is U_nR', and compounds of formula **I-A-ii**, **I-B-ii**, and **I-C-ii** are provided:





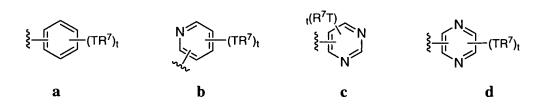


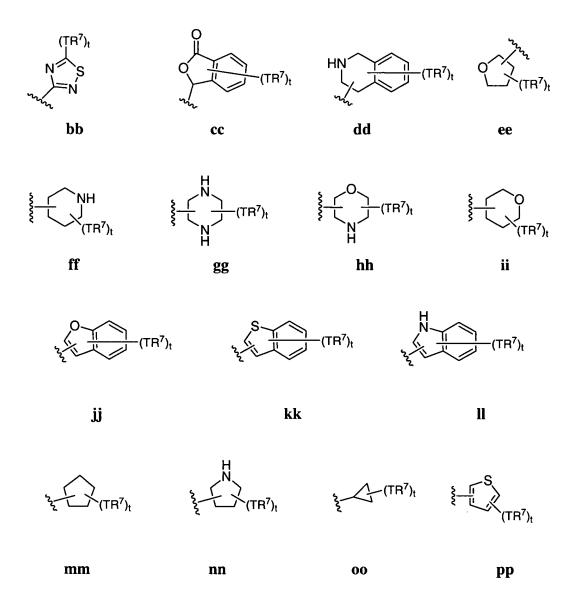
I-A-ii

I-B-ii

I-C-ii.

- 14. The compound of claim 13, wherein Q^3 is a direct bond, or is $-(CHR^6)_q$ -, $-(CHR^6)_q$ O-, $-(CHR^6)_q$ S(O)₂-, $-(CHR^6)_q$ S(O)₋, $-(CHR^6)_q$ NR-, or $-(CHR^6)_q$ C(O)-, wherein q is 0, 1, 2, or 3, and R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}$ V(R)(R'), $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring.
- 15. The compound of claim 14, wherein R⁶ is CH₂OH, CH₂CH₂OH, OH, OMe, OEt, NH₂, NH(Me), NH(Et), N(Me)(Me), CH₂NH₂, CH₂CH₂NH₂, NHCO₂t-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, NH(CH₂)₃NH₂, NH(CH₂)₂NH₂, NH(CH₂)₂NHEt, NHCH₂pyridyl, NHSO₂phenyl, NHC(O)CH₂C(O)Ot-butyl, NHC(O)CH₂NH₃, and NHCH₂-imidazol-4-yl.
- 16. The compound of claim 13, wherein Ar^2 is:





wherein t is 0, 1, 2, 3, 4 or 5, and wherein any Ar^2 is bonded to Q^3 through any substitutable nitrogen or carbon atom, and wherein one or more hydrogen atoms on any substitutable nitrogen or carbon atom is substituted with one or more independent occurrences of TR^7 .

- 17. The compound of claim 16, wherein Ar² is **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **n**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**.
- 18. The compound of claim 16, wherein T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently

replaced by -O-, -NR-, -S-, $-SO_2$ -, -COO-, -CO-, $-OSO_2$ -, $-NRSO_2$, -CONR-, or $-SO_2NR$ -, and R^7 is R' or halogen.

- 19. The compound of claim 16, wherein each occurrence of TR^7 is independently $-C_{1-3}$ alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, -C(O)N(R)(R'), -C(O)N(R)(R'), $-C(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, or $-OSO_2R'$.
- 20. The compound of claim 13, wherein R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic.
- 21. The compound of claim 1, wherein X^1 and X^2 are each independently CR^4 or N, and compounds have one of formulas II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, or XIII:

The compound of claim 21, wherein compounds have one of formulas II-A, II-B, II-C, III-D, III-E, III-F, III-A, III-B, III-C, III-D, III-E, III-F, IV-A, IV-B, IV-C, IV-D, IV-E, IV-F, V-A, V-B, V-C, V-D, V-E, V-F, VI-A, VI-B, VI-C, VI-D, VI-E, VII-F, VIII-A, VIII-B, VIII-C, VIII-D, VIII-E, VIII-F, IX-A, IX-B, IX-C, IX-D, IX-E, IX-F, X-A, X-B, X-C, X-D, X-E, X-F, XI-A, XI-B, XI-C, XI-D, XI-E,

XI-F, XII-A, XII-B, XII-C-, XII-D, XII-E, XII-F, XIII-A, XIII-B, XIII-C, XIII-D, XIII-E, or XIII-F:

III-D

III-C

$$\begin{array}{c|c}
R^1 & R^2 \\
R^2 & R^2 \\
R^2 & N & Q^1
\end{array}$$

$$\begin{array}{c|c}
R^2 & R^3 \\
V-A & V-A
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c}
R^2 \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c}
R^3 \\
IV-B
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^2 \\
R^3
\end{array}$$

$$\begin{array}{c|c}
R^2 \\
R^3 \\
\hline
 IV-D$$

$$\begin{array}{c|c}
R^1 & R^2 \\
R^1 & N & S & R^2 \\
 & N & Q^1 & R^3
\end{array}$$

$$V-C$$

$$\begin{array}{c|cccc}
R^1 & R^2 & R^4 & R^2 \\
R^1 & & & & & & \\
R^2 & & & & & & \\
R^2 & & & & & & \\
R^4 & & & & & & \\
VI-A & & & & & \\
\end{array}$$

$$\begin{array}{c|cccc}
R^1 & & & & & \\
N & N & R^4 & R^2 & & \\
N & & & & & \\
N & & & & & \\
R^2 & & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & \\
N & & & & & \\
N & & & & \\
N & & & & & \\
N &$$

$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^4 \\
\hline
VI-D
\end{array}$$

$$\begin{array}{c|c}
R^1 & R^2 \\
R^1 & R^2 \\
R^2 & R^3 \\
\hline
N & N & Q^1 \\
\hline
N & R^3 \\
\hline
VII-A$$

$$\begin{array}{c|c}
R^1 \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c}
R^2 \\
N \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c}
R^3 \\
VII-E
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
N \\
N \\
N \\
N \\
N \\
N \\
Q^1 \\
R^3 \\
VII-B$$

$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^2 \\
R^4 \\
VII-D
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^2 \\
R^3
\end{array}$$

$$\begin{array}{c|c}
R^2 \\
N \\
N \\
N \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c|c}
R^3 \\
VIII-D
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
N \\
Q^1 \\
R^3 \\
VIII-E$$

$$\begin{array}{c|cccc}
R^1 & R^2 & R^2 \\
R^1 & N & N-S & Q^1 & R^3 \\
\hline
IX-C
\end{array}$$

$$\begin{array}{c|cccc}
R^1 & & & & & \\
N & N & R^4 & R^2 & & \\
N & N & N & N & Q^1 & R^3 \\
R^Z & N - S & & & & & \\
IX-E & & & & & & \\
\end{array}$$

$$\begin{array}{c|cccc}
R^1 & & & & & & \\
N & N & R^4 & R^2 & & & \\
R^1 & & & & & & \\
R^2 & N-S & & & & & \\
IX-B & & & & & & \\
\end{array}$$

$$\begin{array}{c|cccc}
R^1 & R^2 & R^4 & R^2 \\
N & & & & & & & & & & & \\
N & & & & & & & & & & & \\
N & & & & & & & & & & & \\
R^2 & & & & & & & & & & & \\
IX-D & & & & & & & & & & \\
\end{array}$$

X-B

$$\begin{array}{c|cccc}
R^1 & & & & & \\
N & N & R^4 & R^2 & & \\
N & N & N & N & N
\end{array}$$

$$\begin{array}{c|cccc}
R^2 & & & & & \\
R^2 & & & & & \\
R^4 & & & & & \\
X-E & & & & & \\
\end{array}$$

$$\begin{array}{c|c}
R^1 & R^2 \\
R^1 & R^2 \\
R^2 & R^3 \\
R^4 & XI-A
\end{array}$$

$$\begin{array}{c|c}
R^1 & R^2 \\
R^1 & N & R^2 \\
R^1 & N & N & R^3 \\
\hline
R^4 & XI-C
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
N \\
Q^1 \\
R^3 \\
XI-E$$

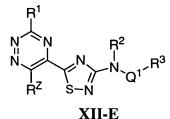
$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^4
\end{array}$$

$$\begin{array}{c}
R^2 \\
R^3
\end{array}$$

$$\begin{array}{c}
R^3 \\
X-D
\end{array}$$

$$\begin{array}{c|c}
R^1 \\
R^2 \\
R^2 \\
R^4
\end{array}$$
XI-D





$$\begin{array}{c|c}
R^1 \\
N \\
Q^1 \\
R^3 \\
XII-F$$

$$\begin{array}{c|cccc}
R^1 & R^2 & R^4 & R^2 \\
R^1 & & & & & & & & & & \\
R^1 & & & & & & & & & & & \\
R^2 & & & & & & & & & & & \\
XIII-A & & & & & & & & & & \\
\end{array}$$

$$\begin{array}{c|cccc}
R^1 & & & & & \\
N & & & & & & R^2 \\
N & & & & & & & & & \\
N & & & & & & & & & \\
R^2 & & S-N & & & & & & & \\
XIII-D & & & & & & & & \\
\end{array}$$

- 23. The compound of claim 1, wherein each occurrence of R^1 is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OR, SR, or $N(R)_2$.
- 24. The compound of claim 23, wherein each occurrence of R^1 is independently hydrogen, halogen, -CH₃, -CH₂CH₃, -OH, -OCH₃, -SCH₃, -NH₂, -N(CH₃)₂, -N(CH₂CH₃)₂, NH(CH₂)₂NHCH₃, NH(cyclopropyl), NH(CH₂)cyclopropyl, or NH(CH₂)₂N(CH₃)₂.
- 25. The compound of claim 1, wherein each occurrence of R^Z is independently hydrogen, halogen, C_1 - C_4 aliphatic, OH, OR', or N(R)(R').
- 26. The compound of claim 25, wherein each occurrence of R^Z is independently hydrogen, halogen, Me, OH, OMe, NH₂, or N(Me)₂.
- 27. The compound of claim 1, wherein R^4 groups are each independently hydrogen, C_1 . 6aliphatic, CN, COR, C(=O)OR, C(=O)N(R)₂, or halogen.
- 28. The compound of claim 1, wherein one occurrence of R⁴ is CN and compounds have the general structure II-a:

29. The compound of claim 1, wherein R⁴ is hydrogen and compounds have the general structure III-a:

III-a

30. The compound of claim 1, wherein one occurrence of R^4 is hydrogen and the other occurrence of R^4 is -COOR and compounds have the general structure VI-a:

VI-a

31. The compound of claim 1, wherein R⁴ is hydrogen and compounds have the general structure VII-a:

$$\begin{array}{c|c}
R^1 \\
N \\
Z^1 \\
Z^2 \\
Z^3
\end{array}$$

$$\begin{array}{c|c}
R^2 \\
N \\
N \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c|c}
R^3 \\
\end{array}$$

VII-a

32. The compound of claim 1, wherein one occurrence of R^4 is hydrogen and the other occurrence of R^4 is C(=O)OR and compounds have the general structure **X-a**:

X-a

33. The compound of claim 1, wherein R⁴ is hydrogen and compounds have the general structure **XI-a**:

$$\begin{array}{c|c}
R^1 \\
N \\
Z^1 \\
Z^2 \\
Z^3
\end{array}$$

$$\begin{array}{c|c}
R^2 \\
N \\
N \\
Q^1
\end{array}$$

$$\begin{array}{c|c}
R^3 \\
\end{array}$$

XI-a

34. The compound of claim 1, wherein Q^1 is -CO-, Q^2 is CHR⁶, q is 1 2, or 3, and compounds have one of formulas XIV, XV, or XVI:

35. The compound of claim 1, wherein Q^1 is -CO-, Q^2 is CHR⁶, q is 1, 2 or 3, and compounds have one of formulas **XVII**, **XVIII**, or **XIX**:

$$\begin{array}{c|c}
R^1 & R^2 & R^6 \\
R^1 & R^2 & R^6 \\
R^2 & R^4 & R^4
\end{array}$$
XIX

- 36. The compound of claims 34 or 35, wherein compound variables are selected from one of more of the following groups:
- a) each occurrence of R^1 is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OR, SR, or $N(R)_2$;
- b) each occurrence of R¹ is independently hydrogen, halogen, -CH₃, -CH₂CH₃, -OH, -OCH₃, -SCH₃, -NH₂, -N(CH₃)₂, -N(CH₂CH₃)₂, NH(CH₂)₂NHCH₃, NH(cyclopropyl), NH(CH₂)cyclopropyl, or NH(CH₂)₂N(CH₃)₂;
- c) each occurrence of R^Z is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OH, O(R'), or N(R)(R');
- d) each occurrence of R² is independently hydrogen, halogen, Me, OH, OMe, NH₂, or N(Me)₂;
- e) R^2 is hydrogen, or is U_nR' , where n is 1, and U is- CH_2 -, - CH_2CH_2 -, - CH_2CH_2 CH₂-, - CH_2CH_2 -, - CH_2CH_2 -, - CH_2CH_2 -, - CH_2 -, and R' groups are hydrogen, C_1 -C4-alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R', taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered heterocyclyl ring;
- f) each occurrence of R⁴ is independently hydrogen, C₁₋₆aliphatic, CN, COR, COOR, CON(R)₂, or halogen;
 - g) q is 1, 2, or 3;
- h) R^6 is R', -N(R)(R'), $-(CH_2)_{1-4}N(R)(R')$, -OR', $-(CH_2)_{1-4}OR'$, $-NR(CH_2)_{1-4}N(R)(R')$, $-NR(CH_2)_{1-4}SO_2R'$, $-NR(CH_2)_{1-4}COOR'$, or $-NR(CH_2)_{1-4}COR'$, or two occurrences of R^6 .

taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered saturated, partially unsaturated, or fully unsaturated ring;

- i) R⁶ is CH₂OH, CH₂CH₂OH, OH, OMe, OEt, NH₂, NH(Me), NH(Et), N(Me)(Me), CH₂NH₂, CH₂CH₂NH₂, NHCO₂t-butyl, phenyl, cyclopentyl, methyl, ethyl, isopropyl, cyclopropyl, NH(CH₂)₃NH₂, NH(CH₂)₂NH₂, NH(CH₂)₂NHEt, NHCH₂pyridyl, NHSO₂phenyl, NHC(O)CH₂C(O)Ot-butyl, NHC(O)CH₂NH₃, and NHCH₂-imidazol-4-yl;
- j) Ar¹ is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C_{1-6} alkylidene chain wherein one or two methylene units are optionally and independently replaced by $-O_{-}$, $-NR_{-}$, $-S_{-}$, $-SO_{2-}$, $-COO_{-}$, $-CO_{-}$, $-COO_{-}$, $-COO_{-}$, $-COO_{-}$, $-NRSO_{2-}$, $-CONR_{-}$, or $-SO_{2}NR_{-}$, and R^{7} is R' or halogen; or
- k) Ar^1 is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}$ alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)_2N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, CON(R)(R'), or $-OSO_2R'$.
- 37. The compound of claim 34 or 35, q is 1, and Ar¹ is optionally substituted phenyl and compounds of general formula XIV-A through XIX-A are provided:

wherein:

each occurrence of R¹ is hydrogen;

each occurrence of RZ is hydrogen;

R² is hydrogen, or is U_nR', where n is 1, and U is–CH₂-, -CH₂CH₂-, -CH₂CH₂-CH₂-, -CH₂CH₂-, -CH₂-CH₂-, and R' groups are hydrogen, C₁-C₄alkyl, optionally substituted tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridinyl, phenyl, or cyclohexyl, or R and R', taken together with the nitrogen atom to which they are bound, form an optionally substituted 5- or 6-membered heterocyclyl ring;

each occurrence of R^4 is independently hydrogen, $C_{1\text{-}6}$ aliphatic, CN, COR, COOR, CON(R)₂, or halogen;

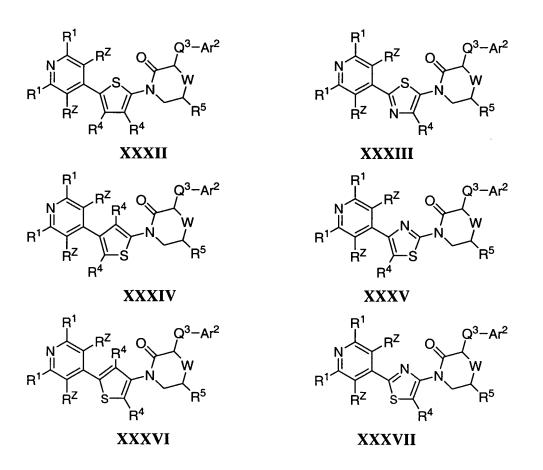
 R^6 is R', -N(R)(R'), -(CH₂)₁₋₄N(R)(R'), -OR', -(CH₂)₁₋₄OR', -NR(CH₂)₁₋₄N(R)(R'), -NR(CH₂)₁₋₄SO₂R', -NR(CH₂)₁₋₄COOR', or -NR(CH₂)₁₋₄COR'; and

t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1-3}$ alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, -C(O)N(R)(R'), $-(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, CON(R)(R'), or $-OSO_2R'$.

38. The compound of claim 1, wherein R^2 and Q^1 - R^3 , taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have the general formula **XX** through **XXV**:

39. The compound of claim 1, R^2 and Q^1 - R^3 , taken together with the atoms to which they are bound form a 5-membered cyclic group, and compounds have the general formula **XXVI** through **XXXI**:

40. The compound of claim 1, wherein R^2 and Q^1 - R^3 , taken together with the atoms to which they are bound form a 6-membered cyclic group, and compounds have the general formula **XXXII** through **XXXVII**:



wherein W is O, NR⁵, or CHR⁵.

- 41. The compound of claims 38, 39 or 40, wherein compound variables are selected from one of more of the following groups:
- a) each occurrence of R^1 is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OR, SR, or $N(R)_2$;
- b) each occurrence of R^Z is independently hydrogen, halogen, optionally substituted C_1 - C_4 aliphatic, OH, OR' or N(R)(R');
- c) each occurrence of R^4 is independently hydrogen, C_{1-6} aliphatic, CN, COR, COOR, CON(R)₂, or halogen;
- d) R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic;
- e) Q^3 is a direct bond, or is $-(CHR^6)_q$ -, $-(CHR^6)_q$ O-, $-(CHR^6)_q$ S-, $-(CHR^6)_q$ S(O)₂-, $-(CHR^6)_q$ S(O)-, $-(CHR^6)_q$ NR-, or $-(CHR^6)_q$ C(O)-, wherein q is 0, 1, 2, or 3; and
- f) Ar² is ring **a, b, e, g, h, i, j, k, n, r, cc, dd, ff, jj, ll**, or **pp**, wherein t is 0, 1, 2, or 3, and T is a bond or is an optionally substituted C₁₋₆ alkylidene chain wherein one or two methylene units are optionally and independently replaced by -O-, -NR-, -S-, -SO₂-,-COO-, -CO-, -OSO₂-, -NRSO₂, -CONR-, or -SO₂NR-, and R⁷ is R' or halogen.
- 42. The compound of claims 38, 39 or 40, wherein compound variables are selected from one of more of the following groups:
- a) each occurrence of R^1 is independently hydrogen, halogen, -CH₃, -CH₂CH₃, -OH, -OCH₃, -SCH₃, -NH₂, -N(CH₃)₂, -N(CH₂CH₃)₂, NH(CH₂)₂NHCH₃, NH(cyclopropyl), NH(CH₂)cyclopropyl, or NH(CH₂)₂N(CH₃)₂;
- b) each occurrence of R^Z is independently hydrogen, halogen, Me, OH, OMe, NH₂, or N(Me)₂;
- c) each occurrence of R⁴ is independently hydrogen, C₁₋₆aliphatic, CN, COR, COOR, CON(R)₂, or halogen;
- d) R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic;

e) Q^3 is a direct bond, or is -(CHR⁶)_q-, -(CHR⁶)_qO-, -(CHR⁶)_qS-, -(CHR⁶)_qS(O)₂-, -(CHR⁶)_qS(O)-, -(CHR⁶)_qNR-, or -(CHR⁶)_qC(O)-, wherein q is 0, 1, 2, or 3; and

f) Ar^2 is ring **a**, **b**, **e**, **g**, **h**, **i**, **j**, **k**, **n**, **r**, **cc**, **dd**, **ff**, **jj**, **ll**, or **pp**, wherein t is 0, 1, 2, or 3, and each occurrence of TR^7 is independently $-C_{1.3}$ alkyl, -OR', -SR', $-CF_3$, $-OCF_3$, $-SCF_3$, -F, -Cl, I, -Br, -COOR', -COR', $-O(CH_2)_4N(R)(R')$, $-O(CH_2)_3N(R)(R')$, $-O(CH_2)_2N(R)(R')$, $-O(CH_2)_4CON(R)(R')$, $-O(CH_2)_3CON(R)(R')$, $-O(CH_2)_2CON(R)(R')$, $-O(CH_2)_4OR'$, $-(CH_2)_3OR'$, $-(CH_2)_2OR'$, $-CH_2OR'$, optionally substituted phenyl or benzyl, -N(R)(R'), $-(CH_2)_4N(R)(R')$, $-(CH_2)_3N(R)(R')$, $-(CH_2)_2N(R)(R')$, $-(CH_2)_2N(R)(R')$, or $SO_2N(R)(R')$, $NRSO_2R'$, CON(R)(R'), or $-OSO_2R'$.

43. The compound of claims 38, 39 or 40, wherein Ar² is optionally substituted phenyl and compounds of general formula **XX-A**, through **XXXVII** are provided:

$$R^1$$
 R^2
 R^4
 R^4
 R^5
 R^4
 R^5
 R^4
 R^5
 R^4
 R^5

XXVI-A

XXVII-A

$$\begin{array}{c|c}
R^1 & Q^3 & (TR^7)_t \\
R^1 & N & N & N & R^5 \\
R^2 & S & O
\end{array}$$

 R^1 R^2 R^2 R^3 R^4 R^2 R^3 R^5 R^5 R^5

XXVIII-A

XXIX-A

$$R^1$$
 R^2
 R^4
 R^5
 R^5
 R^5

$$R^1$$
 R^2
 R^3
 R^4
 R^5
 R^5

XXX-A

XXXI-A

$$R^{1}$$
 R^{2}
 R^{4}
 R^{2}
 R^{4}
 R^{5}
 R^{5}
 R^{4}
 R^{5}
 R^{4}
 R^{5}
 R^{4}
 R^{5}

$$\begin{array}{c|c}
R^1 & Q & Q^3 \\
R^1 & R^2 & Q & Q^3 \\
R^1 & R^2 & N - R^5
\end{array}$$

XXXII-A

XXXIII-A

 R^{1} R^{2} R^{4} R^{5} R^{4} R^{5} R^{4}

XXXVI-A XXXVII-A

44. The compound of claim 43, wherein compound variables are selected from: each occurrence of R¹ is hydrogen; each occurrence of R² is hydrogen;

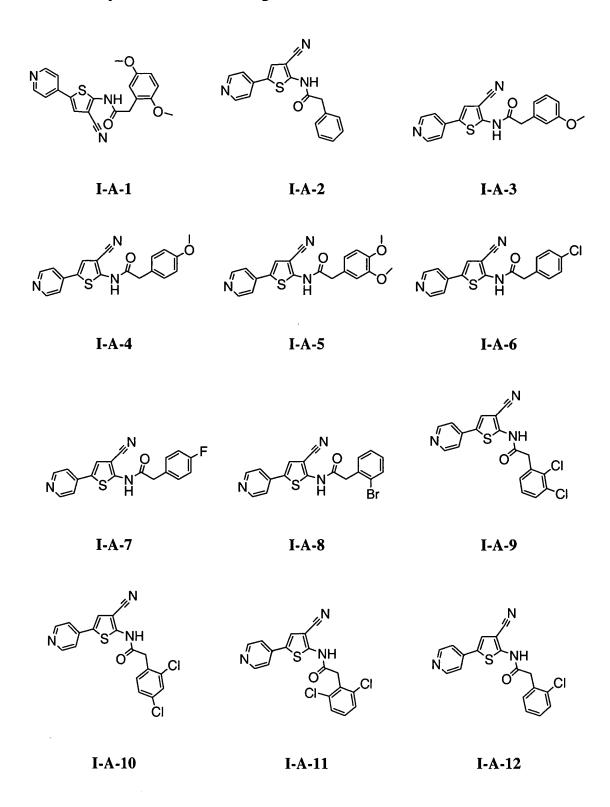
each occurrence of R^4 is independently hydrogen, $C_{1\text{-}6}$ aliphatic, CN, COR, COOR, CON(R)₂, or halogen;

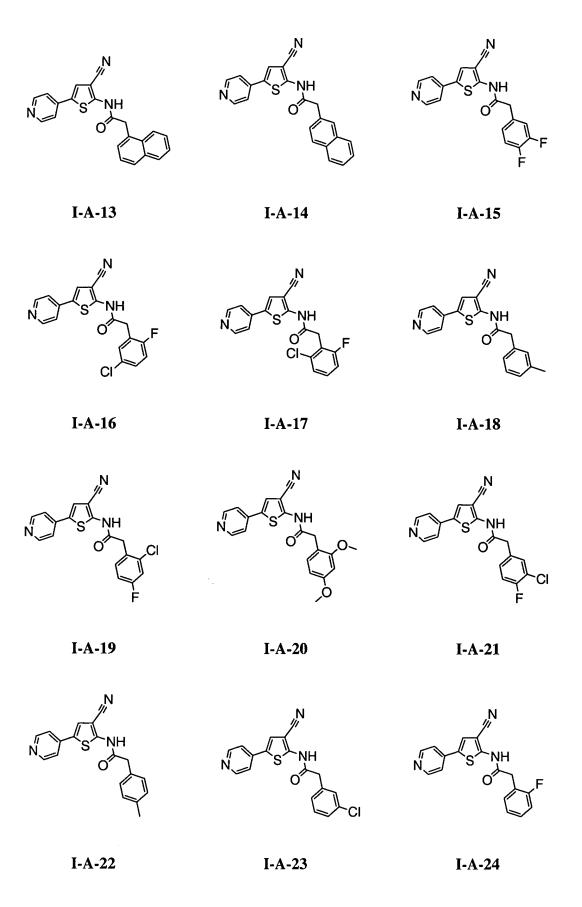
 R^5 is hydrogen, $(CH_2)_3OR'$, $(CH_2)_2OR'$, $(CH_2)OR'$, $(CH_2)_3N(R')_2$, $(CH_2)_2N(R')_2$, $(CH_2)N(R')_2$, or C_{1-4} aliphatic;

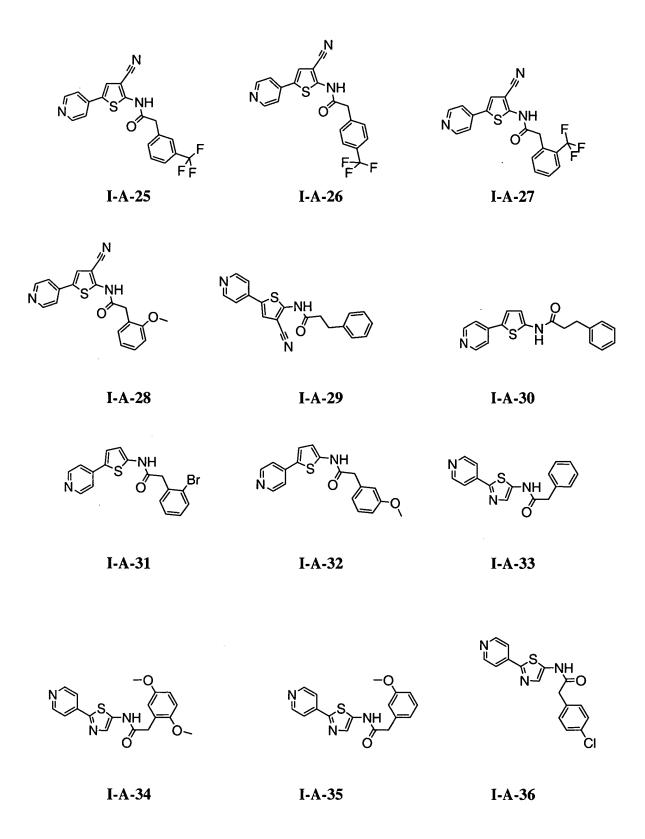
Q³ is a direct bond, or is $-(CHR^6)_{q^-}$, $-(CHR^6)_{q}O_-$, $-(CHR^6)_{q}S_-$, $-(CHR^6)_{q}S(O)_2$ -, $-(CHR^6)_{q}S(O)_2$ -, $-(CHR^6)_{q}S(O)_2$ -, or $-(CHR^6)_{q}S(O)_2$ -, wherein q is 0, 1, 2, or 3; and

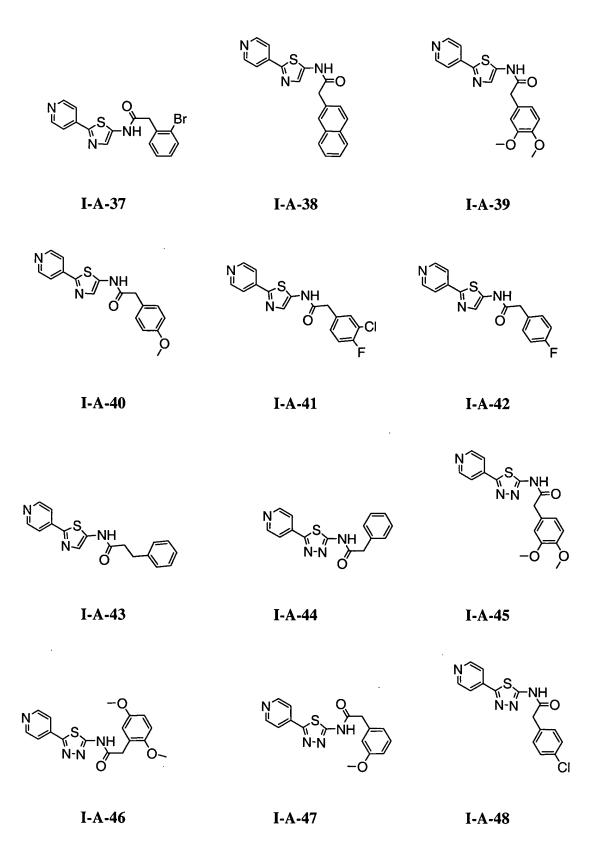
 $t \ is \ 0, \ 1, \ 2, \ or \ 3, \ and \ each \ occurrence \ of \ TR^7 \ is \ independently \ -C_{1-3}alkyl, \ -OR', \ -SR', \ -CF_3, \ -OCF_3, \ -SCF_3, \ -F, \ -Cl, \ I, \ -Br, \ -COOR', \ -O(CH_2)_4N(R)(R'), \ -O(CH_2)_3N(R)(R'), \ -O(CH_2)_2N(R)(R'), \ -O(CH_2)_4CON(R)(R'), \ -O(CH_2)_3CON(R)(R'), \ -O(CH_2)_2CON(R)(R'), \ -O(CH_2)_2CON(R)(R'), \ -O(CH_2)_2CON(R)(R'), \ -O(CH_2)_2CON(R)(R'), \ -O(CH_2)_2CON(R)(R'), \ -C(CH_2)_3OR', \ -(CH_2)_4OR', \ -(CH_2)_3OR', \ -(CH_2)_4N(R)(R'), \ -(CH_2)_4N(R)(R'), \ -(CH_2)_3N(R)(R'), \ -(CH_2)_2N(R)(R'), \ -(CH_2)N(R)(R'), \ or \ SO_2N(R)(R'), \ NRSO_2R', \ -CON(R)(R'), \ or \ -OSO_2R'.$

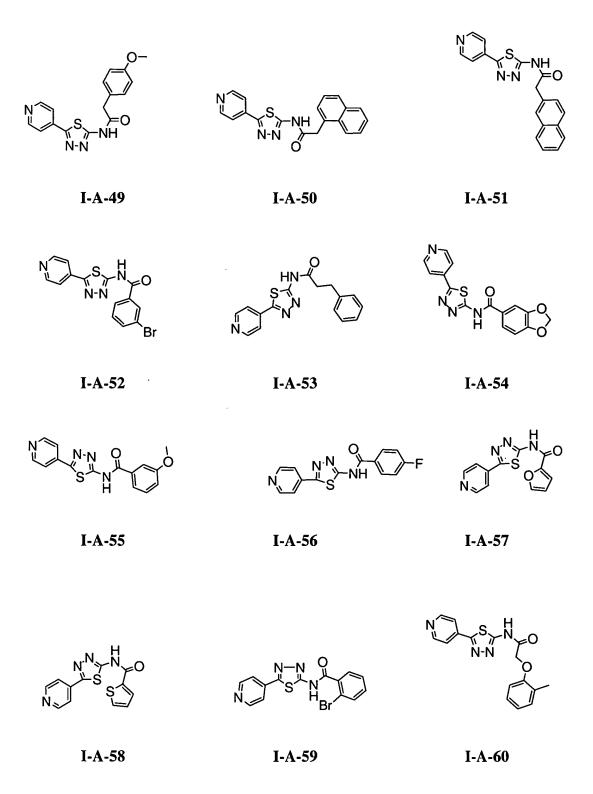
45. The compound of claim 1, having one of the structures:

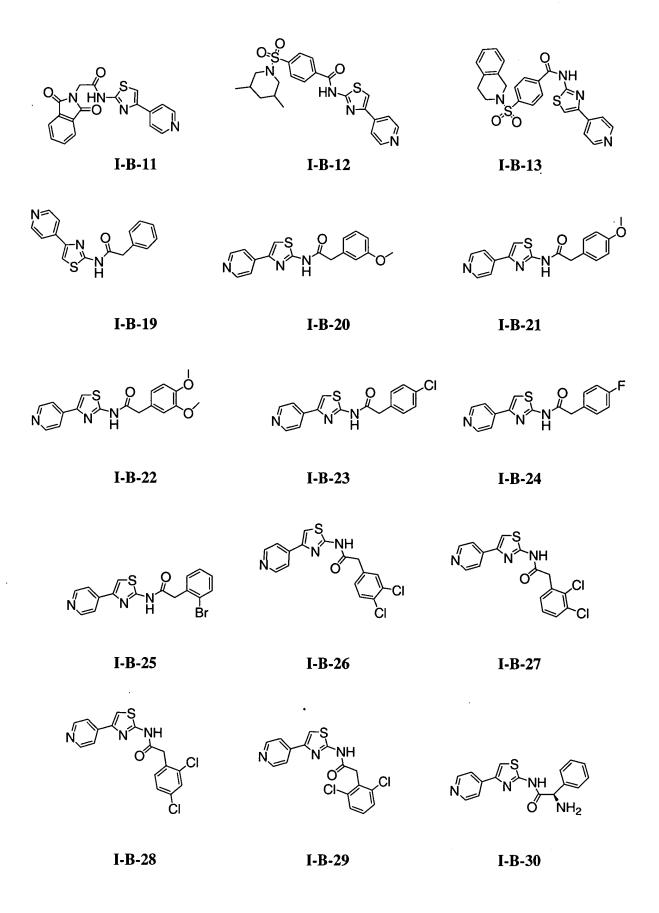


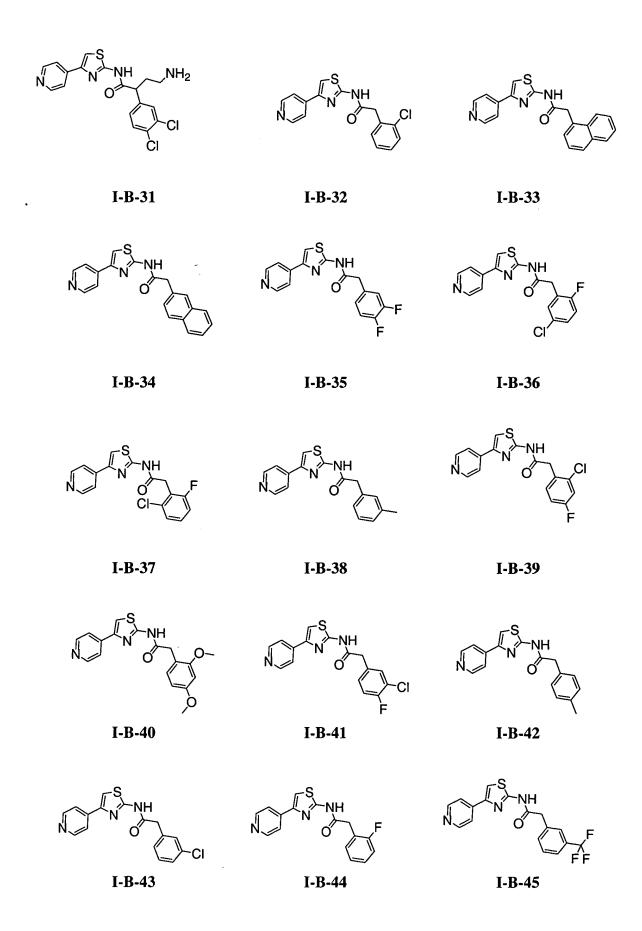


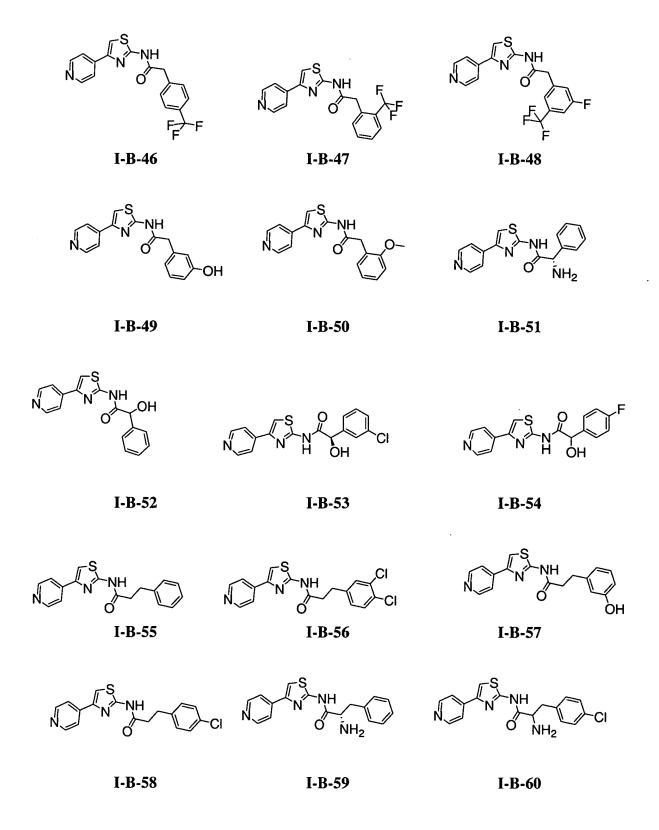


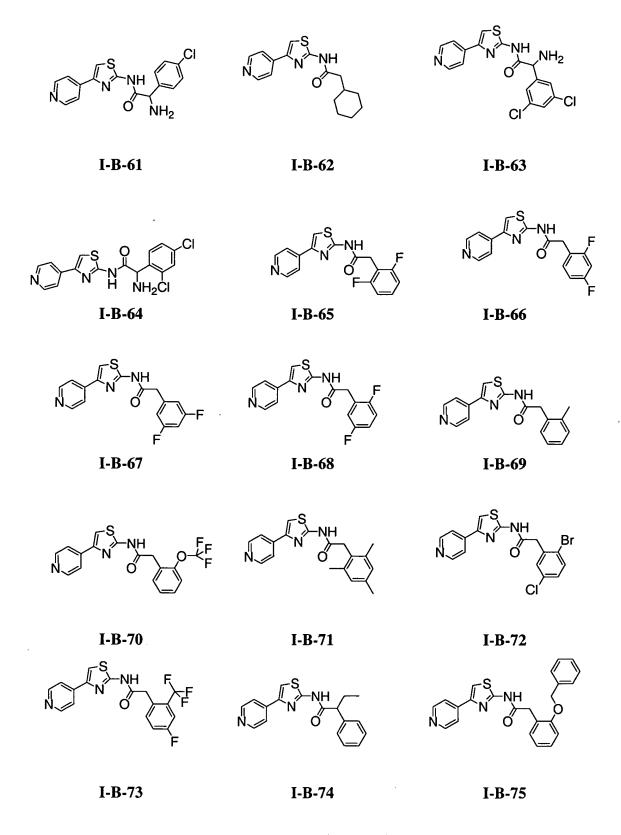


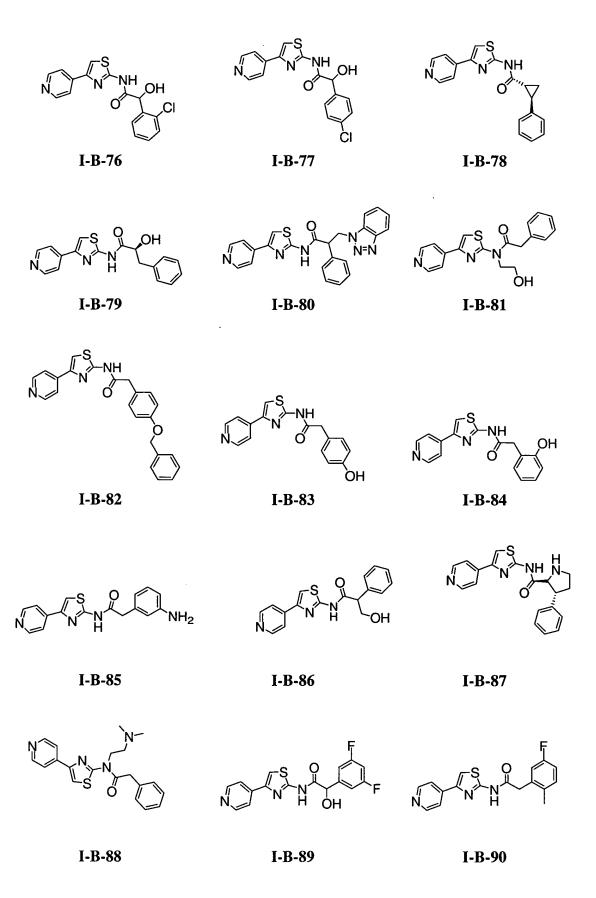


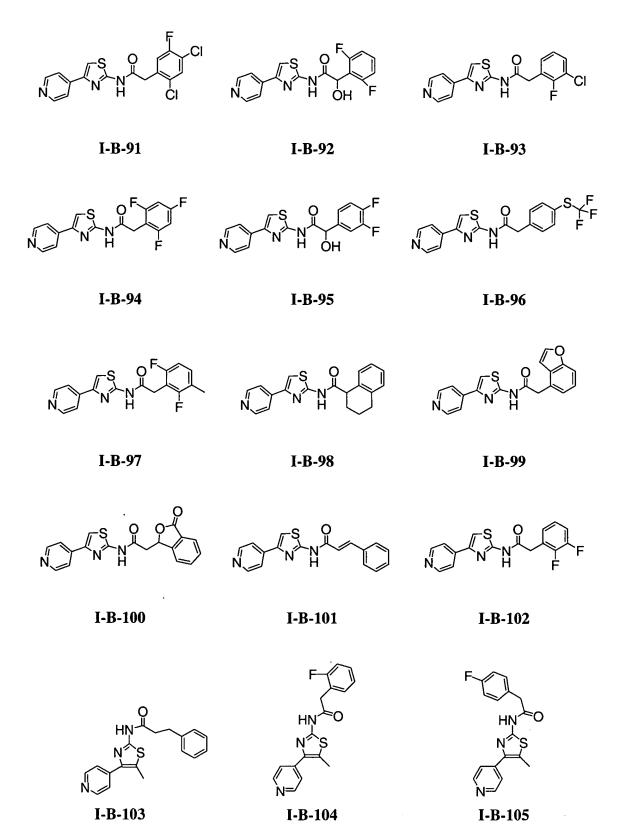


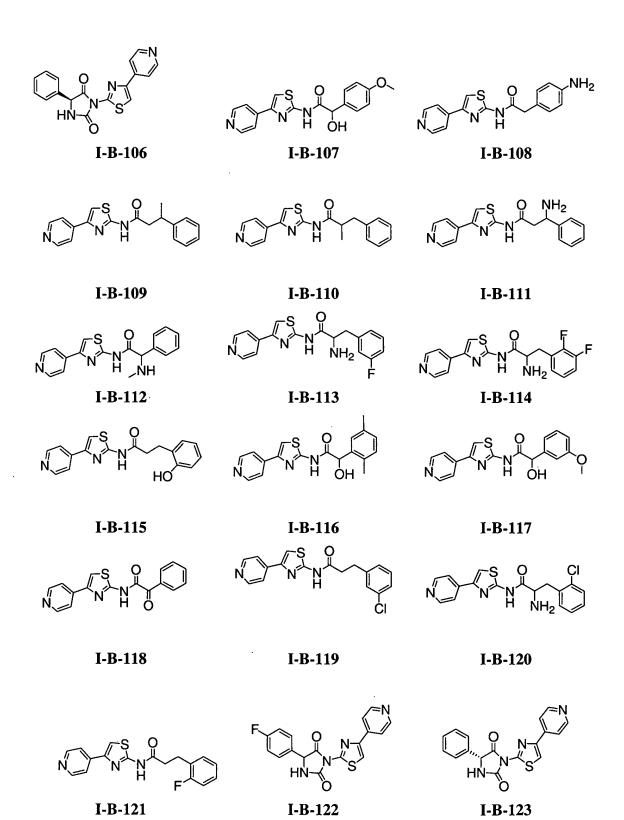


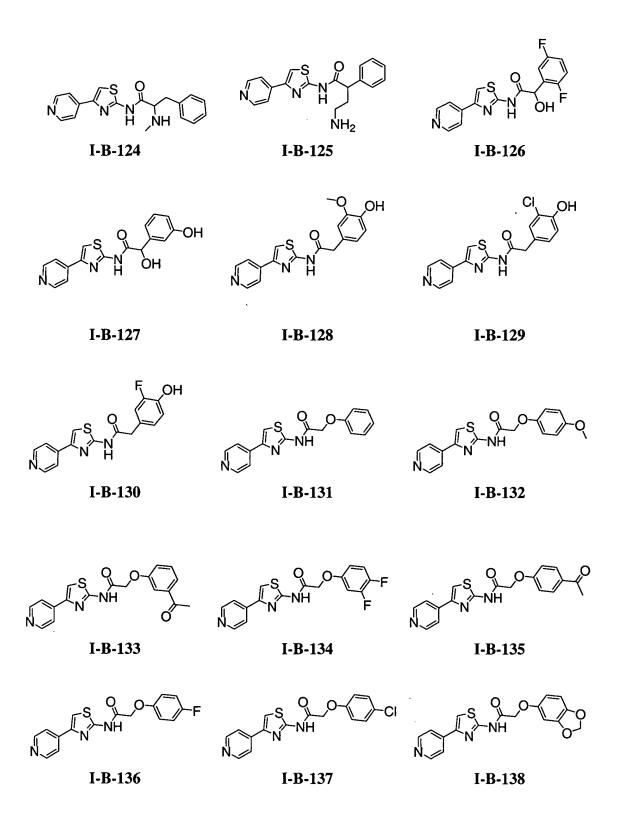


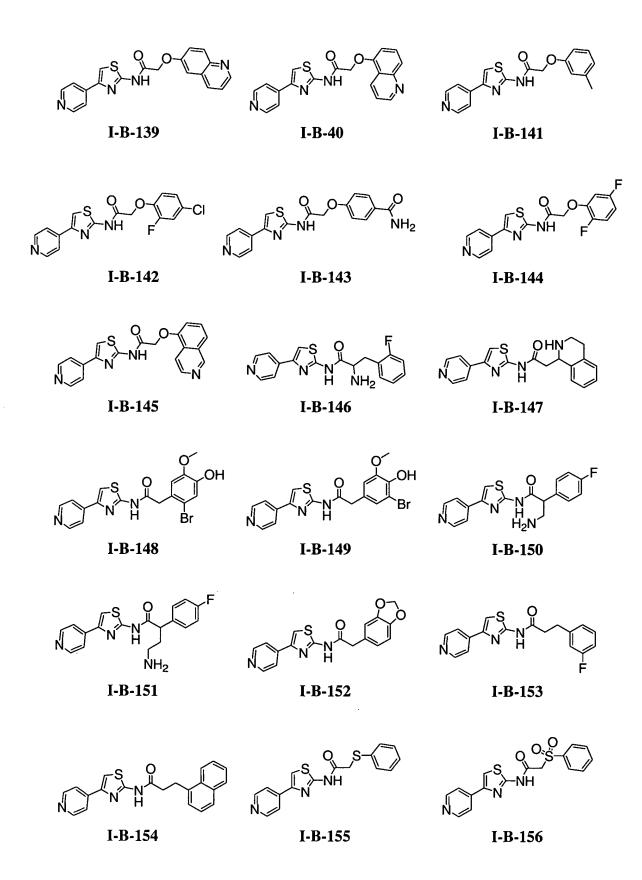


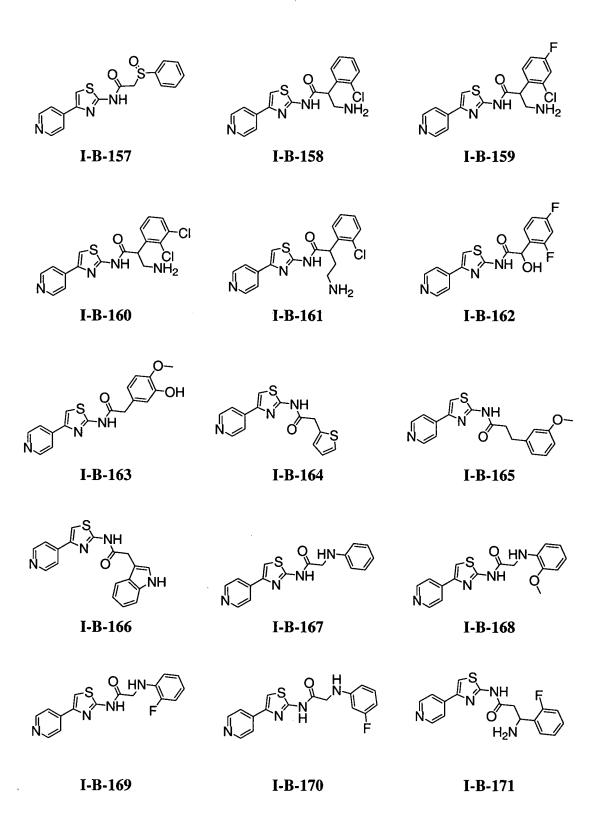


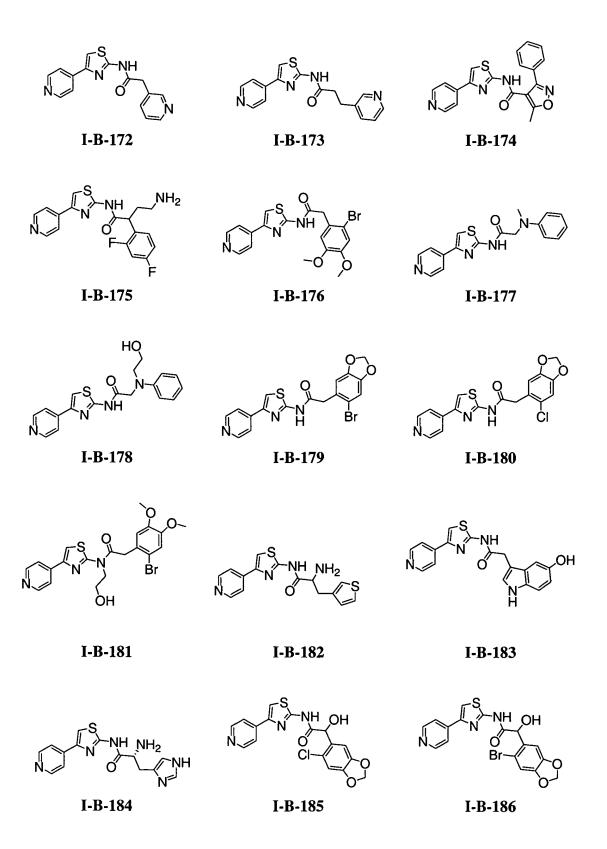


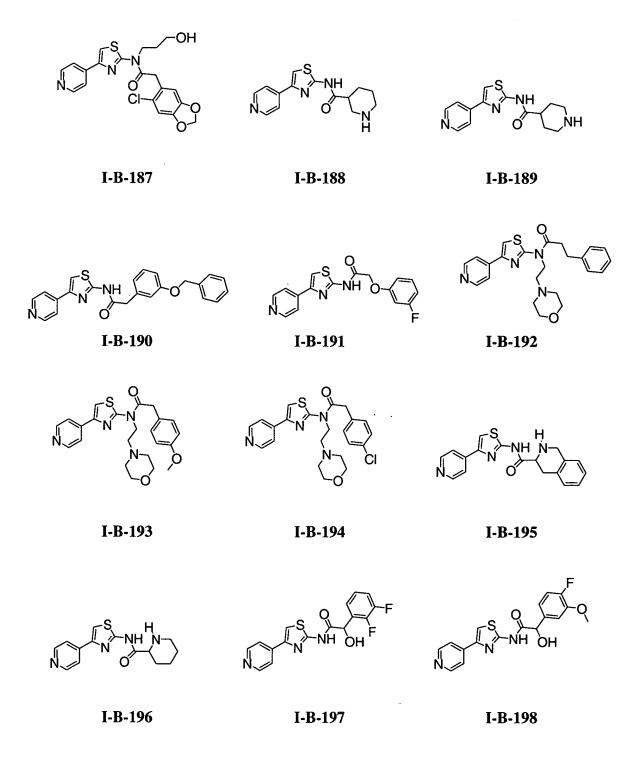


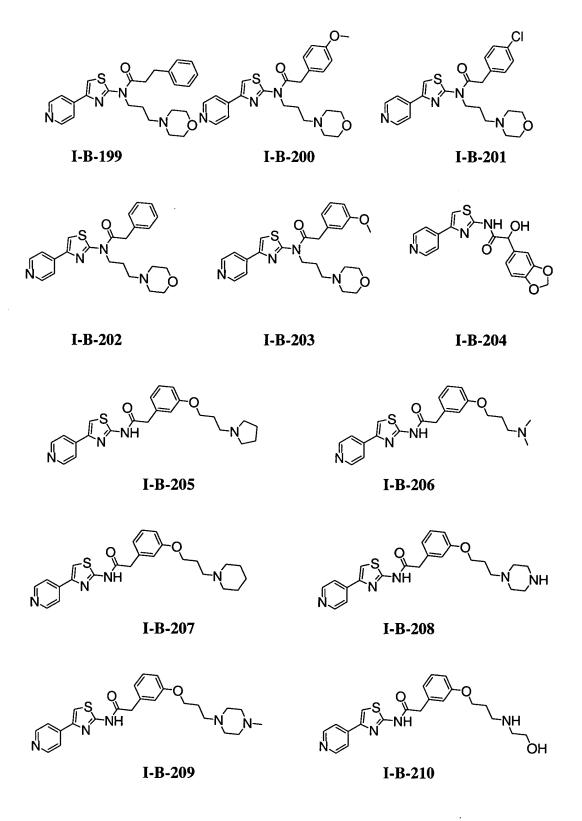


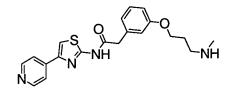












N NH NH OH

I-B-211

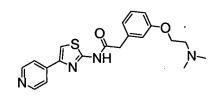
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I-B-213

I-B-214

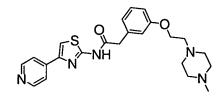
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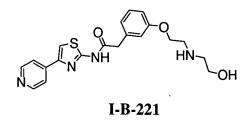
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I-B-218



I-B-219

I-B-220



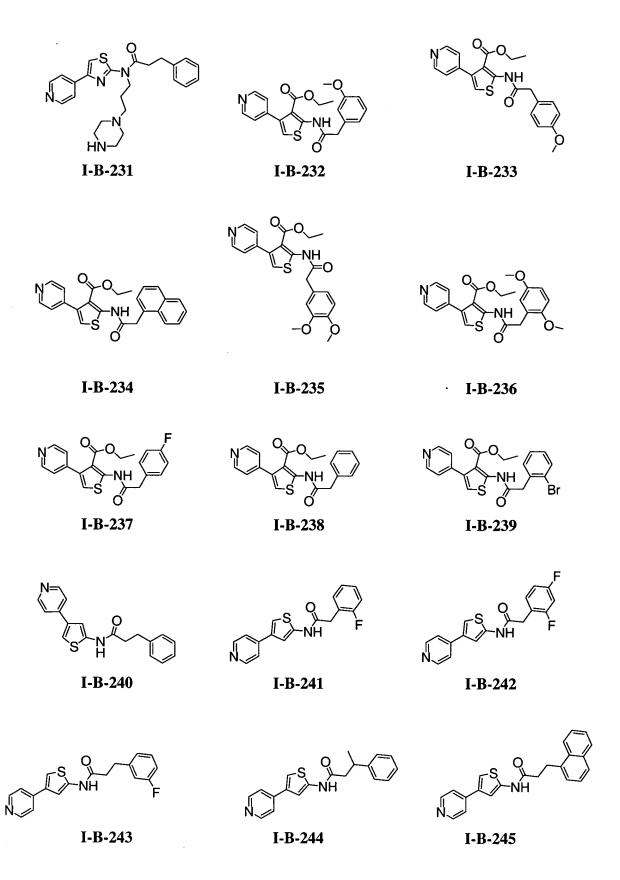
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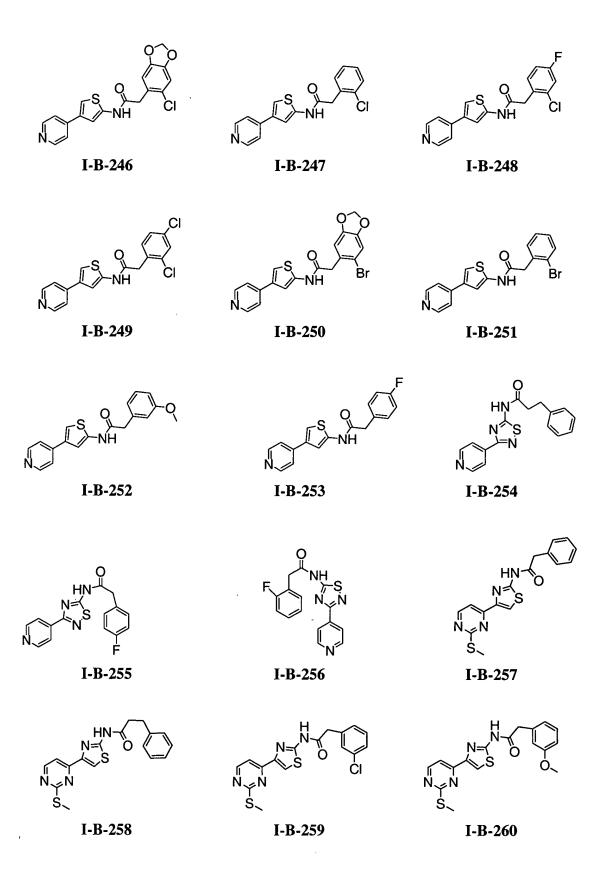
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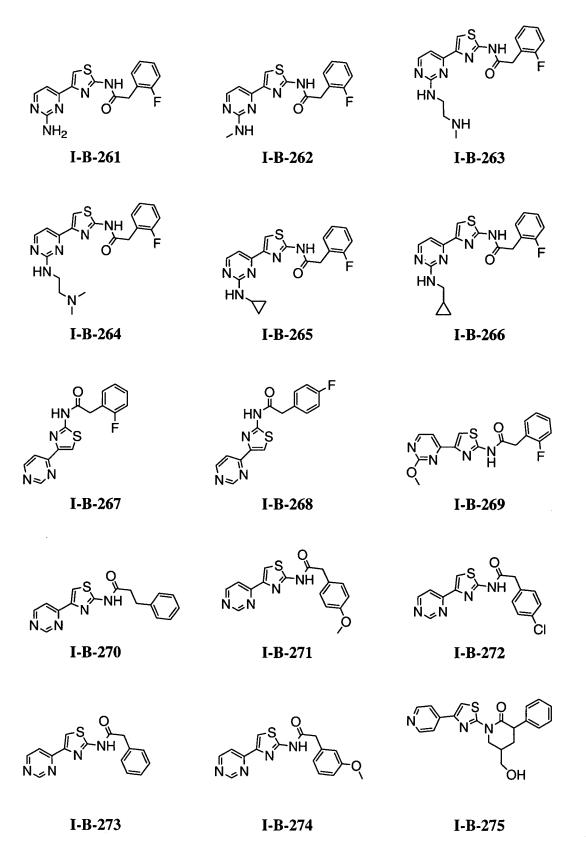
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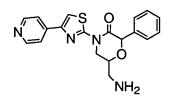
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I-B-230









N N NH

I-B-276

I-B-277

I-B-278

I-B-279

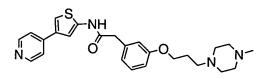
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I-B-280

I-B-281

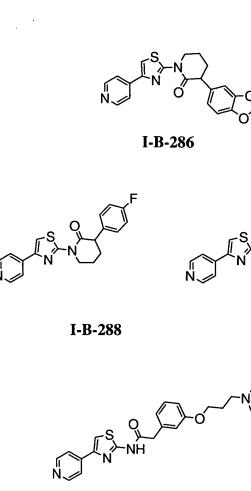
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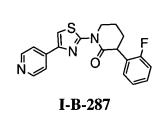
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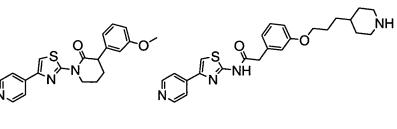


I-B-284

I-B-285

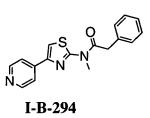


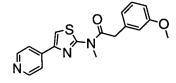




I-B-292 I-B-291

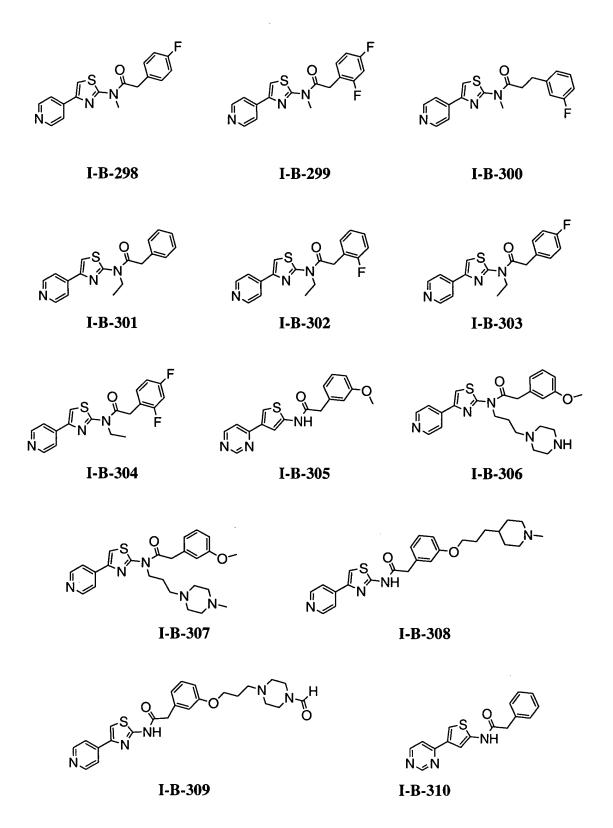
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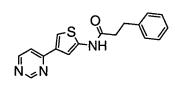




I-B-290

I-B-295 I-B-296 I-B-297





I-B-311

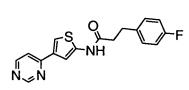
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I-B-313

I-B-314

I-B-315

I-B-316



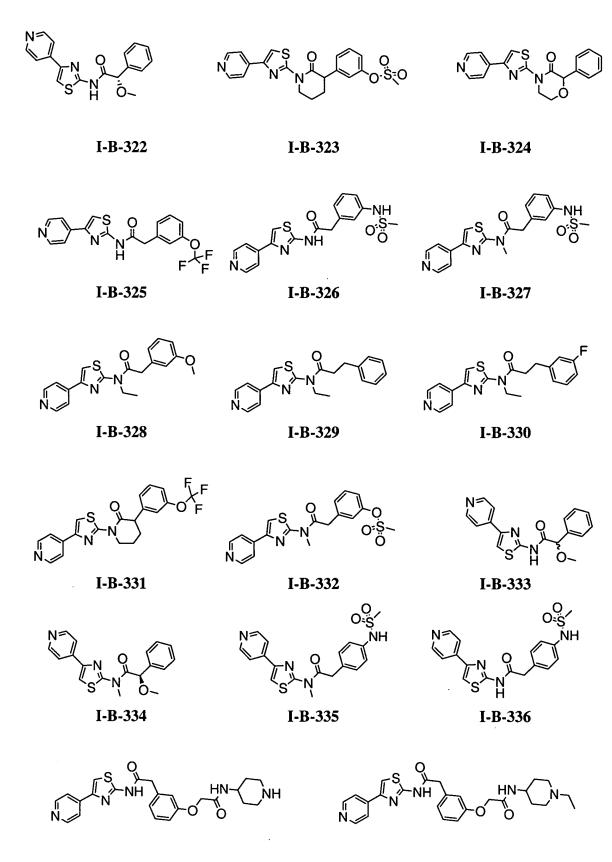
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I-B-318

I-B-319

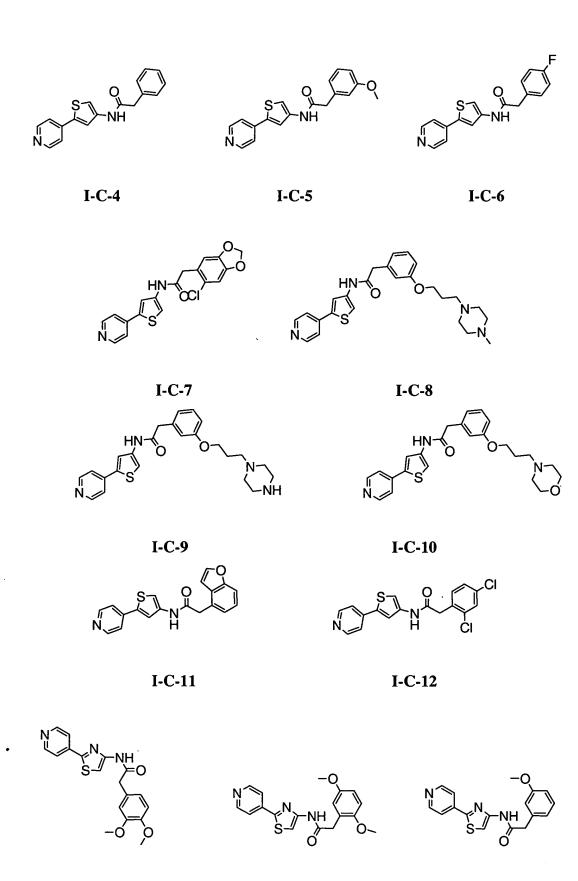
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I-B-321

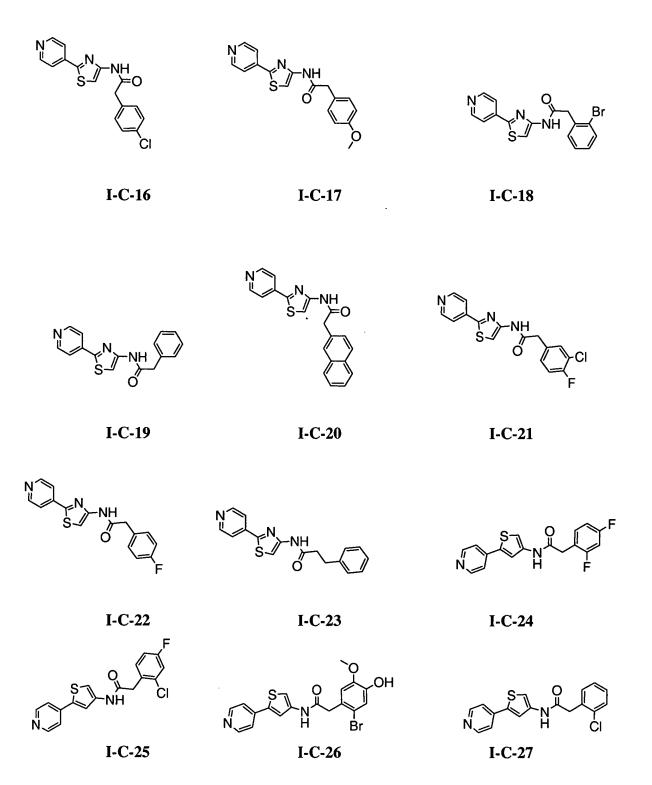


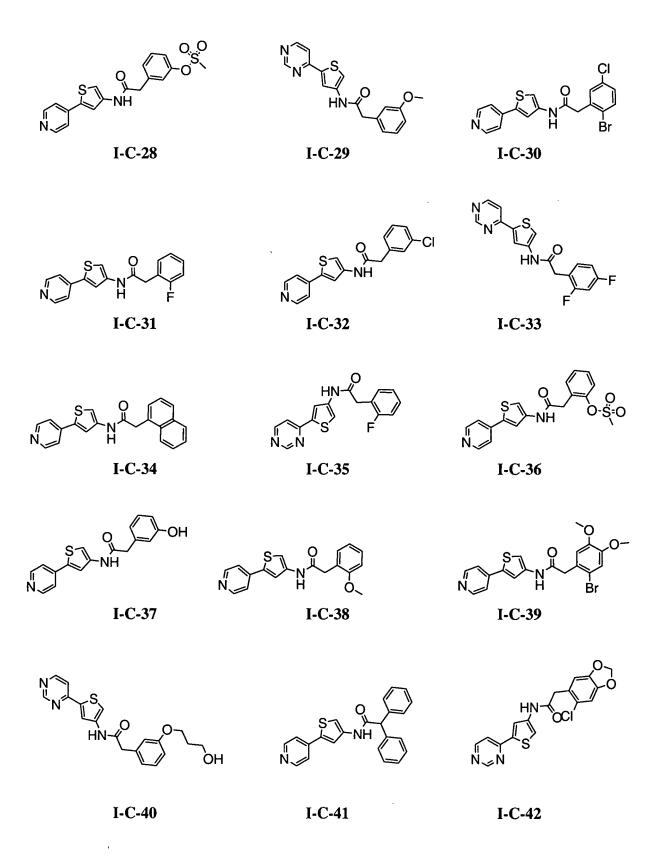
I-B-337

I-B-338



I-C-13 I-C-15





- 46. A composition comprising an effective amount of compound of claim 1, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
- 47. The composition of claim 46, additionally comprising a therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.
- 48. A method of inhibiting ROCK, ERK, GSK, or AGC kinase activity in:
 - (a) a patient; or
 - (b) a biological sample;

which method comprises administering to said patient, or contacting said biological sample with a compound having the formula:

or a pharmaceutically acceptable salt thereof, wherein:

wherein
$$A_1$$
 is $A_2 - A_1$, $A_1 - S$, or $A_2 - A_1$;

R¹ is halogen, CN, NO₂, or V_mR;

 Z^1 and Z^3 are each independently N or CR^2 , and Z^2 is N or CR^1 , provided that Z^1 , Z^2 and Z^3 are not simultaneously N;

each occurrence of RZ is independently halogen, CN, NO2, or UnR';

 R^2 is U_nR' ;

X¹ and X² are each independently CR⁴ or N;

each occurrence of R⁴ is independently halogen, CN, NO₂, or V_mR;

each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -OCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-;

m and n are each independently 0 or 1;

each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; Q^1 is -CO-, $-SO_2$ -, -CONR-, or $-SO_2NR$ -; R^3 is Q^2 - Ar^1 ,

or R² and Q¹-R³, taken together with the nitrogen atom, form the cyclic group:

, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO₂-, -O-, -S-, -NR⁵-, or -C(R⁵)₂-, and R⁵ is U_nR^3 ;

 Q^2 and Q^3 are each independently a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by -NR'-, -S-, -O-, -CS-, $-CO_2$ -, -OCO-, -COCO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2$ -, $-SO_2NR'$ -, $-NR'SO_2$ -, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, $-NR'SO_2NR'$ -, -SO-, $-SO_2$ -, $-PO_2$ -, or -POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, CN, NO_2 , or U_nR' , or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar¹ and Ar² are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ and Ar² are each optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁-C₆ alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -NRCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R⁷ is independently R', halogen, NO₂, or CN; or a pharmaceutically acceptable salt or composition thereof.

- 49. The method of claim 48, wherein the method comprises inhibiting ROCK activity.
- 50. A method of treating or lessening the severity of a disease condition or disorder selected from a proliferative disorder, a cardiac disorder, a neurodegenerative disorder, a psychotic disorder, an autoimmune disorder, a condition associated with organ transplant, an

inflammatory disorder, an immunologically mediated disorder, a viral disease, or a bone disorder, comprising the step of administering to said patient a compound having the formula:

$$\begin{array}{c|cccc}
R^1 & & & & \\
N & Z^1 & & R^2 \\
Z^2 & Z^3 & & & & & \\
\hline
I & & & & & & \\
I & & & & & & \\
\end{array}$$

or a pharmaceutically acceptable salt thereof, wherein:

wherein is
$$X_2-X_1$$
, X_1-S , or $S-X_1$;

R¹ is halogen, CN, NO₂, or V_mR;

 Z^1 and Z^3 are each independently N or CR^2 , and Z^2 is N or CR^1 , provided that Z^1 , Z^2 and Z^3 are not simultaneously N;

each occurrence of R^Z is independently halogen, CN, NO₂, or U_nR';

 R^2 is U_nR' ;

 X^1 and X^2 are each independently CR^4 or N;

each occurrence of R⁴ is independently halogen, CN, NO₂, or V_mR;

each occurrence of U or V is independently an optionally substituted C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are optionally and independently replaced by -NR-, -S-, -O-, -CS-, $-CO_2$ -, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO-, -NRCO-, -NRCO-, -NRSO-, -NRSO-,

m and n are each independently 0 or 1;

each occurrence of R is independently hydrogen or an optionally substituted C_{1-6} aliphatic group; and each occurrence of R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, a 3-8-membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or R and R', two occurrences of R, or two occurrences of R', are taken together with the atom(s) to which they are bound to form an optionally substituted 3-12

membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; Q^1 is -CO-, $-SO_2$ -, -CONR-, or $-SO_2NR$ -; R^3 is Q^2 - Ar^1 ,

or R² and Q¹-R³, taken together with the nitrogen atom, form the cyclic group:

5² N Q³ Ar²

, where s is 1 or 2, each occurrence of Y is independently, as valency and stability permit, -CO-, -CS-, -SO₂-, -O-, -S-, -NR⁵-, or -C(R⁵)₂-, and R⁵ is U_nR^7 ;

 Q^2 and Q^3 are each independently a bond or a C_{1-6} alkylidene chain, wherein up to two methylene units of the chain are each optionally and independently replaced by -NR'-, -S-, - O-, -CS-, $-CO_2$ -, -OCO-, -CO-, -COCO-, -CONR'-, -NR'CO-, $-NR'CO_2$ -, $-SO_2NR'$ -, - $NR'SO_2$ -, -CONR'NR'-, -NR'CONR'-, -OCONR'-, -NR'NR'-, $-NR'SO_2NR'$ -, -SO-, $-SO_2$ -, -PO-, $-PO_2$ -, or -POR'-; and wherein any carbon atom in the one or more methylene units is optionally substituted with one or two occurrences of R^6 , wherein each occurrence of R^6 is independently halogen, CN, NO_2 , or U_nR' , or two occurrences of R^6 , or R' and R^6 , taken together with the atoms to which they are bound, form an optionally substituted 3-6-membered cycloalkyl, heterocyclyl, aryl or heteroaryl ring; and

Ar¹ and Ar² are each independently a 5-8 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein Ar¹ and Ar² are each optionally substituted with 0-5 independent occurrences of TR⁷; wherein T is a bond or is a C₁-C₆ alkylidene chain wherein up to two methylene units of T are optionally and independently replaced by –NR-, -S-, -O-, -CS-, -CO₂-, -OCO-, -CO-, -COCO-, -CONR-, -NRCO-, -NRCO₂-, -SO₂NR-, -NRSO₂-, -CONRNR-, -NRCONR-, -NRCONR-, -NRNR-, -NRSO₂NR-, -SO-, -SO₂-, -PO-, -PO₂-, or -POR-; and each occurrence of R⁷ is independently R', halogen, NO₂, or CN;

or a pharmaceutically acceptable salt or composition thereof.

51. The method of claim 50, comprising the additional step of administering to said patient an additional therapeutic agent selected from a chemotherapeutic or anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory or immunosuppressive agent, a neurotrophic factor, an anti-psychotic agent, an agent for treating cardiovascular disease, an agent for treating destructive bone disorders, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

- 52. The method of claim 50, wherein disease, condition, or disorder is allergy, asthma, diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, AIDS-associated dementia, amyotrophic lateral sclerosis (AML, Lou Gehrig's disease), multiple sclerosis (MS), schizophrenia, cardiomyocyte hypertrophy, reperfusion/ischemia (e.g., stroke), baldness, cancer, hepatomegaly, cardiovascular disease including cardiomegaly, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, inflammation, hypertension, angina pectoris, cerebrovascular contraction, peripheral circulation disorder, premature birth, arteriosclerosis, vasospasm (cerebral vasospasm, coronary vasospasm), retinopathy, erectile dysfunction (ED), AIDS, osteoporosis, Crohn's Disease and colitis, neurite outgrowth, or Raynaud's Disease.
- 53. The method of claim 50, wherein disease, condition, or disorder is atherosclerosis, hypertension, erectile dysfunction (ED), reperfusion/ischemia (e.g., stroke), or vasospasm (cerebral vasospasm and coronary vasospasm).